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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,453	01/03/2006	Eugene Tedeschi	PA1751	8045

28390 7590 02/21/2008

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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
02/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

rs.vasciplegal@medtronic.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,453	TEDESCHI, EUGENE	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,11,12,14,17,19-22 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 11-12, 14, 17, 19-22, 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after non-final rejection filed on December 11, 2007 is acknowledged. Claims 5-10, 13, 15-16, 18, 23-24 have been cancelled, and new claims 26-28 have been added. Applicant elected without traverse of proteasome inhibitor species bortezomib and the polymer species acrylic polymers and copolymers in the reply filed on July 27, 2007. Claims 1-4, 11-12, 14, 17, 19-22, and 25-28 are pending in this office action.

Withdrawn Objections and Rejections

1. The objection to the tile is hereby withdrawn due to Applicant's arguments.

2. The objection to the specification is hereby withdrawn due to Applicant's amendment to the specification.

3. Rejection of claim 6 under 35 U.S.C. 112, second paragraph, as being indefinite is hereby withdrawn due to Applicant's cancellation of claim 6.

4. Rejection of claims 1, 4, 6-8, 12, 20-21 and 23-25 under 35 U.S.C. 102(e) are hereby withdrawn due to Applicant's amendment to the claims and arguments.

In the previous office action, the species acrylic polymers and copolymers were indicated as being free of prior art. On further examination, prior art was found for this species. Therefore, a non-final office action follows below.

Maintained Revised Rejection

5. 5.The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-4, 11-12, 14, 17, 19-22, 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epstein SE (US 2004/0116329) as evidenced by Adams J (Expert Opinion Ther. Patents, 2003, 13(1): 45-57) in view of Palasis et al (PG Pub 2004/0106987).

The instant claims are drawn to a medical device for delivering an anti-restenotic composition comprising a stent coated with a polymer comprising an acrylic polymer or copolymer wherein said polymer has bortezomib incorporated therein and the polymer delivers the bortezomib into a tissue of a mammal.

As described in the previous office action, Epstein SE teaches inhibition of restenosis of blood vessels by administering to the cells in the blood vessel walls a compound, e.g., a protein or small molecule, capable of inhibiting the ubiquity-

proteasome protein degradation pathway. The inhibiting compound is preferably administered by coating the compound on a stent and implanting the stent in the blood vessel after angioplasty (see abstract). The reference further teaches inhibition of cell proliferation, particularly smooth muscle cells in arterial walls is achieved by inhibiting ubiquitin-proteasome protein degradation pathway, thereby interfering with proliferation of cells that could contribute to restenosis (see paragraph [0028]). The reference further teaches that LDP-341 is described as a proteasome inhibitor (see paragraph [0037]). As evidenced by Adams J, the proteasome inhibitor bortezomib (Velcade) is also known as PS-341, MLN-341 and LDP-314 (see p. 45, 2nd paragraph). The reference claims an intravascular stent coated with a compound capable of inhibiting the ubiquitin-proteasome protein degradation pathway in a cell (see claim 5) and the stent of claim 5 wherein said compound is LDP-341 (see claim 6). This reads on claims 1, 4 and 12. Furthermore, the reference claims a method of preventing cell proliferation in blood vessel walls after angioplasty comprising administering to at least one cell in a blood vessel wall after an angioplastic procedure an amount of compound capable of inhibiting the ubiquitin-proteasome protein degradation pathway in the cell effective to prevent proliferation of the cell, wherein the compound is LDP-341 coated on a stent and implanting the stent within the blood vessel (see claims 1-4). This reads on claims 20-21 and 25. The reference teaches that compound administered via a stent-based platform, by achieving high local concentrations at the vessel wall and low systemic concentrations, will be effective with minimal systemic side effects (see paragraph [0039]). The reference further teaches that any stent coating that has the proper release

kinetics for the proteasome inhibiting protein, small molecule, or gene encoding such a product, and that allows for viable incorporation of such a molecule, and that allows for such product to reside in the coating for days or weeks, will be appropriate (see paragraph [0044]). The reference is silent as to the shape of the stent, however, the reference discloses that the stent is implanted into the blood vessel, and therefore, is tubular, and because it is tubular, it would have a cylindrical shape having an outer and an inner surface. The differences between the reference and the instant claims are that the reference does not teach expandable stent, acrylic polymer, balloon catheter, the concentration of 0.1% to 99% by weight of proteasome inhibitor to polymer, and delivery of proteasome inhibitor to a site at risk using injection catheter.

However, Palasis et al teach a medical devices for delivery of therapeutic agents and at least one polymeric layer, which typically acts to control the release of the therapeutic agent from the medical device (see abstract). The reference further teaches that biostable polymeric covering layers include those that comprise one or more of the following: polyolefin polymers (see paragraph [0016]), acrylic polymers (including methacrylic polymers and copolymers (see paragraph [0088]). The reference teaches balloon-expandable or self-expandable medical device (stents) (see paragraph [0059]). The reference teaches that one advantage of the polymer coated medical devices such as stents, containing therapeutic agents can be provided in which the rate of release of the therapeutic agents is adequately regulated so as to provide a therapeutically effective amount of such agent over a desired period of time (see paragraph [0032], the polymer resists cracking upon expansion of the medical device (see paragraph [0033]),

the therapeutic agent is not substantially disrupted during medical device manufacture (see paragraph [0034]), and can be provided in which the uptake of the therapeutic agent by the targeted tissue is enhanced (see paragraph [0035]). The reference further teaches that the polymer coated endovascular stent having a conventional frame, such as tubular shape, and permits the stent to self-expand or to expand to the desired shape after an expansive force is applied, for example, by the expansion of a balloon within the stent (see paragraph [0061]). The reference teaches that a coating is applied on the surface of each stent, and the coating can include either a biostable or biodisintegradable polymer which contains or is provided as a coating over a therapeutic agent (see paragraph [0062]). Furthermore, the reference teaches that numerous therapeutic agents that have been identified as candidates for vascular treatment regimens, such as agents targeting restenosis can be used on the medical device, including proteasome inhibitor (see paragraph [0072]).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Palasis et al and Epstein SE, since they both teach a medical device, stent (with a coating that has a proper release kinetics), delivering a therapeutic agent (especially to inhibit restenosis) to the treatment site. There is a motivation to combine the teachings since both prior arts teach stents coated with therapeutic agents, and Palasis et al teach that coating the therapeutic agent with polymer provide adequate control of the release of the therapeutic agent. Furthermore, Palasis et al also teach that proteasome inhibitors can also be used as a therapeutic agent. There is a reasonable expectation of success, since devices as stents have limited surface areas

(see Palasis paragraph [0007]), and thus polymer coating containing a therapeutic agents will provide adequate control of the release of that therapeutic agent (see paragraph [0010]). Additionally, polymer coated medical devices such as stents, containing therapeutic agents can be provided in which the rate of release of the therapeutic agent is adequately regulated over desired period of time (paragraph [0032]); the polymer resists cracking upon expansion of the medical device (paragraph [0033]); structural integrity of the therapeutic agent is maintained (paragraph [0034]); uptake of the therapeutic agent by the targeted tissue is enhanced (see paragraph [0035]).

Furthermore, it has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, "When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

The "problem" facing those in the art was alleviating restenosis after surgical intervention by means of balloon angioplasty or bypass grafting, and there were a limited number of methodologies available to do so, for example, a catheter delivery systems and coated stents to deliver proteins or small molecules (coating impregnate with therapeutic agents). The skilled artisan would have had reason to try these

methodologies with the reasonable expectation that at least one would be successful. In this case, LDP-341 is a proteasome inhibitor, and coating the stent with polymer can provide therapeutically effective amount of agent over a desired period of time, polymer coated stents resist cracking upon expansion of the medical device, therapeutic agent's structural integrity is maintained during the manufacture of the device when coated with polymer, and the uptake of the therapeutic agent by the targeted tissue is enhanced due to polymer, and both were useful for inhibiting restenosis. Thus, inhibiting restenosis using bortezomib (proteasome inhibitor) coated within a polymer (acrylic or copolymer) in a concentration of between 0.1% to 99% by weight on a stent is "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Response to Applicant's Arguments

8. Applicant argues that "the Examiner has stated on page 2, section 1 of the Office Action dated September 11, 2007 that the elected species of acrylic polymer as the polymer coating the surface of the stent, appears to be free of prior art, and that the Applicant has amended the claims to recite acrylic polymers and copolymers."

9. Applicant's arguments have been fully considered but have not been found persuasive, because upon further consideration of the prior art (specifically Palasis et al), the species of acrylic polymer for coating the stent has been found, as describe above. Therefore, Applicant's arguments are moot.

Rejection-35 U.S.C. 112, 1st

New Matter Rejection

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 27-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

The claims are drawn to a medical device wherein the medical device (vascular stent) delivers an anti-restenotic effective amount of a second proteasome inhibitor. The claims in question recite "a second proteasome inhibitor".

Lack of Ipsis Verbis Support

The specification is void of any literal support for the "effective amount of a second proteasome inhibitor" claimed. In the context of second proteasome inhibitor, the word "second" in relation to proteasome inhibitor is not present anywhere in the specification. The words "another" and "additional" were searched in the context of "second proteasome inhibitor", however, those words were not found in the context of proteasome inhibitor anywhere in the specification. The phrase "effective amount of a second proteasome inhibitor" was not found in the specification. The phrase "at least one proteasome inhibitor" was found throughout the specification (see for example,

paragraph [0047]). However, this is not in the context of "effective amount of a second proteasome inhibitor".

Lack of Implicit or Inherent Support

"While there is not in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Thus support can be furnished implicitly or inherently for a specifically claimed limitation. However, the specification lacks any implicit or inherent support for the claimed "effective amount of a second proteasome inhibitor". As explained supra, there is no support for any concept of "second" proteasome inhibitor in the specification. Examples only describe one proteasome inhibitor (bortezomib) incorporated into the polymer. For example, Example 2 describes bortezomib-THF suspension mixed with polycaprolactone (PCL), and this form a drug/polymer solution. This stent is coated with the drug/polymer solution to form the polymer-drug coated stent. Example 3 describes the PVP-bortezomib-PVP sandwich type coating. Examples 4 and 5 also describe the polymer-bortezomib coated stents. Additionally, there are no examples that state a medical device that delivers an effective amount of a second proteasome inhibitor in addition to bortezomib.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Fri, 5:30 AM to 3:00 PM.

14. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Anish Gupta/

Primary Examiner, Art Unit 1654